Addressing resistance to antibiotics in systematic reviews of antibiotic interventions

Leonard Leibovici[1*], Mical Paul[2], Paul Garner[3], David J. Sinclair[3], Arash Afshari[4], Nathan Leon Pace[5], Nicky Cullum[6], Hywel C. Williams[7], Alan Smyth[8], Nicole Skoetz[9], Chris Del Mar[10], Anne G.M. Schilder[11], Dafna Yahav[1], David Tovey[12]

[1]Department of Medicine E, Beilinson Hospital, Rabin Medical Center, Petah-Tiqva; and Sackler Faculty of Medicine, Tel-Aviv University, Israel

[2]Division of Infectious Diseases, Rambam Health Care Campus, Haifa; and Technion-Israel Institute of Technology and the Ruth & Bruce Rappaport Faculty of Medicine, Haifa

3 Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, UK

[4]Rigshospitalet, Department of Anaesthesiology, Mother & Children's Section, University of Copenhagen, Copenhagen, Denmark

[5]Cochrane Anaesthesia, Critical and Emergency Care Group, Copenhagen, Denmark; and Department of Anesthesiology, University of Utah, Salt Lake City, UT 84132-2304, USA

[6] Cochrane Wounds Group; and School of Nursing, Midwifery & Social Work, University of Manchester, Manchester, UK

[7] Centre of Evidence Based Dermatology, Faculty of Medicine & Health Sciences, University of Nottingham, Notingham, UK

[8]Cochrane Cystic Fibrosis and Genetic Disorders Group; and Division of Child Health, Obstetrics & Gynaecology, University of Nottingham, Notingham, UK

[9] Cochrane Haematological Malignancies Group; and Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany

[10] Cochrane Acute Respiratory Infections Group; and Centre for Research in Evidence Based Practice, Bond University, Gold Coast, Queensland, Australia

[11]Cochrane ENT Group; and Ear Institute, University College London, London' UK

[12]Cochrane Editorial Unit, London, UK

*Corresponding author: tel: +972 3 9376501; fax: +972 3 9376512; e-mail: leibovic@post.tau.ac.il.

Abstract

Antibiotics are among the most important interventions in healthcare. Resistance of bacteria to antibiotics threatens their effectiveness. Systematic reviews of antibiotic treatments often do not address resistance to antibiotics even when data are available in the original studies. This creates a skewed view, which emphasizes short term efficacy and ignores the long term consequences to the patient and other people.

We offer a framework for addressing antibiotic resistance in systematic reviews. We suggest that the data on background resistance in the original trials should be reported and taken into account when interpreting results. Data on emergence of resistance (whether in the body reservoirs or in the bacteria causing infection) are important outcomes. Emergence of resistance should be taken into account when interpreting the evidence on antibiotic treatment in randomized controlled trials or systematic reviews.

Introduction

Antibiotics are one of the most important interventions in healthcare, substantially reducing mortality and morbidity in severe bacterial infections. Many medical procedures could not be safely performed without antibiotics. Resistance of microorganisms to antibiotics threatens to undo these gains, and there is convincing evidence that consumption of antibiotic drugs induces resistance.[1]

Guidelines and clinical decisions are frequently based on systematic reviews. Between June 2014 and June 2015 approximately 140 systematic reviews on antibiotic treatment were published. However systematic reviews on antibiotic treatment often did not address resistance to antibiotics even when data were available in the original trials.[2] The major cost of antibiotic treatment is probably the harm to future patients from emergence of resistance.[3-5] If emerging resistance is ignored in systematic reviews, readers are presented with a skewed view, stressing short-term efficacy and ignoring the long term consequences to the patient and other people.

Fighting the rise in antibiotic resistance is a global concern. The WHO has recently endorsed a global action plan on antimicrobial resistance with "…five strategic objectives: (i) to improve awareness and understanding of antimicrobial resistance; (ii) to strengthen knowledge through surveillance and research; (iii) to reduce the incidence of infection; (iv) to optimize the use of antimicrobial agents; and (v) to ensure sustainable investment in countering antimicrobial resistance."[6] Considering resistance to antimicrobials in systematic reviews and in the original trials can address at least three of these goals. Authors of systematic reviews can join this effort. This article outlines a framework for addressing resistance to antibiotics in systematic reviews.

Which systematic reviews?

The types of antibiotic interventions where resistance should be considered are detailed in Figure 1. We have selected these interventions (and comparisons) based on the potential divergent influence of the two arms on promoting resistance.

There are three main steps in the expansion of resistance that might be influenced by antibiotic interventions: induction of resistant bacteria in the patient treated with antibiotic drugs; selection of resistant strains in the individual treated; and spread of the resistant bacteria to other people and the surroundings. Because of randomized controlled trials' short timescale only induction and selection of resistant

strains are relevant for most systematic reviews on antibiotic treatment. But for some interventions both induction and selection of resistance and also spread can be addressed (e.g. large scale use of antibiotics in a community.[7]

Baseline resistance and its influence on outcomes

To be useful to policy development, systematic reviews of antibiotic interventions must consider the influence of antibiotic resistance on the wider applicability of the review results. Development of resistance over time might lower the efficacy of drugs tested in old trials. New antibiotics will appear superior to old ones if only evaluated in areas with resistance to the old comparator drug, where the (old) comparator drug is failing. Comparison of a new, broad spectrum antibiotic drug with an old drug for which resistance is more abundant adds little to our understanding if the efficacy of the drugs is not compared in the sub-group of patients with susceptible pathogens.

A systematic review may include studies that were done a long time ago; or done only in certain regions, with local profiles of resistance. Reviewers need to take these differences into account when interpreting their results and discussing their applicability. They should refer to current patterns of resistance and their distribution. In Figure 2 we make recommendations regarding the data that should be sought and extracted from primary studies into systematic reviews and considered in their interpretation. If data are missing, systematic description of the absence of important information in the primary studies will encourage those embarking on new primary studies to consider collecting important information relevant to resistance.

Resistance as an outcome

During antibiotic treatment bacteria resistant to the administered drug have an advantage and might grow in the main non-sterile reservoirs of the body, such as the bowel, naso-pharynx, and skin. Documentation of such changes demands surveillance cultures during and after the trial. This is not done in many trials, as it requires resources, and is an additional burden imposed onto the participants. However in some trials surveillance cultures were done;[2] and the results can be incorporated in systematic reviews.

Data on super-imposed bacterial infections by pathogens resistant to the study antibiotic during or shortly after treatment should be collected as outcomes. Even if

susceptibilities to antibiotics were not reported, bacterial infections during antibiotic treatment suggest resistance to the antibiotic drug. Emergence of resistance in the index pathogen (initially susceptible) during treatment is rare in acute infections but important when it occurs. However, in some cases treatment is given for chronic infection, where eradication of the organism is unlikely, (for example anti-pseudomonal antibiotics for lung infection in cystic fibrosis). It is particularly important to report resistance data in systematic reviews in these conditions, as treatment is often lifelong and selection of resistant organisms is commonplace.[8]

In studies in which a whole population or group of people were exposed to an antibiotic intervention (for example azithromycin for trachoma[7] or decontamination of the oropharynx and intestinal tract in intensive care units,[9] the changes in resistance over time in the population are important and should be collected. Figure 3 details the data that should ideally be gathered on resistance as outcome in trials of antibiotic interventions.

Conclusions

Not all trials report data relevant to antibiotic resistance. Where trials report resistance these data should be extracted, analysed and used in the interpretation of systematic reviews. Where data on antibiotic resistance are not available, the implications of resistance should be considered in the discussion section. Systematic reviews can point to areas where crucial data on resistance are missing from the original studies, setting a research agenda.

We offer a framework for data collection and discussion. The same considerations apply to systematic reviews on anti-viral and anti-fungal agents.

We aim to draw on this framework in the development of Cochrane protocols and reviews. We hope that the use of this framework in systematic reviews will encourage researchers to include reference to resistance in the design of their trials and in their reports. We also hope that the readers of these systematic reviews will look for data on resistance and incorporate them in their decisions on treatment and policy.

Transparency declaration

Mical Paul, Paul Garner and Leonard Leibovici developed a framework for taking resistance to antibiotics into account in systematic reviews. The framework was further developed in discussions and correspondence by all authors. The effort was supported by the Cochrane Editorial Unit. All authors contributed to the final form of the article. The guarantor is Leonard Leibovici.

The authors have no conflict of interest to report.

Funding

The article was prepared as part of our routine work, and we received no funding.

References

1. Bell BG, Schellevis F, Stobberingh E, et al. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis* 2014; **14**:13.

2. Leibovici L, Soares-Weiser K, Paul M, et al. Considering resistance in systematic reviews of antibiotic treatment. *J Antimicrob Chemother* 2003; **52**:564-7.

3MacGowan A. Clinical implications of antimicrobial resistance for therapy. *J Chemother* 2008; **62**:105-114.

4.Smith R, Coast J. The true cost of antimicrobial resistance. *BMJ* 2013;**346**:f1493.

5.Leibovici L, Shraga I, Andreassen S. How do you choose antibiotic treatment? *BMJ* 1999; **318**:1614-6.

6.Antimicrobial resistance: Draft global action plan on antimicrobial resistance. World I Health Assembly, 27.3.2015. http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_20-

7.West SK, Bailey R, Munoz B, et al. A randomized trial of two coverage targets for mass treatment with azithromycin for trachoma. *PLoS Negl Trop Dis* 2013;**7**:e2415.

8.Elphick HE, Jahnke N. Single versus combination intravenous antibiotic therapy for people with cystic fibrosis. *Cochrane Database Syst Rev* 2014, Issue 4. Art. No.: CD002007.

9.Oostdijk EA, Kesecioglu J, Schultz MJ et al. Effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in ICUs: a randomized clinical trial. *JAMA* 2014; **312**:1429-37.

Figure 1: Systematic reviews that should address resistance to antibiotics

Comparisons between:

- An antibiotic drug versus no treatment, placebo, delayed treatment or a non-antibiotic intervention.
- Antibiotic drugs or combinations of antibiotics.
- Different durations of antibiotic treatment.
- Different dosing of antibiotic drugs.
- Antibiotic de-escalation/ escalation strategies.
- Antibiotic prophylaxis.
- Mass programmes of antibiotic drug administration.
- Interventions to improve antibiotic prescribing.

Figure 2: Contextual data about baseline antibiotic resistance to be considered in systematic reviews

Data to be collected and reported for each trial included in the systematic review:

- Percentage of resistance to the trial drugs in the trial participants.
- Percentage of resistance to the trial drugs at the time and location/s the trials were conducted; and in the populations of interest.
- Alongside the main comparisons of the outcomes of interest in all randomized patients by intention to treat, outcomes should be compared in the sub-groups of patients with isolates susceptible to the antibiotic given in the specific arm; resistant to this antibiotic; and in patients with sterile cultures. Especially in non-inferiority trials, outcomes should be compared in these sub-groups in a per-protocol analysis as well.

Interpretation of results:

- Discuss the results of the systematic review in populations of interest in the context of the present distribution of pathogens and their susceptibility to antibiotics compared to the time and location of the trials included in the review.
- Discuss the efficacy of the drugs in the intent to treat analysis; but also in context of the efficacy in the sub-group of patients with susceptible isolates.

Figure 3: Antibiotic resistance as an outcome to be collected in systematic reviews of antibiotic interventions

Data to be collected:

- Isolation of resistant bacteria from surveillance cultures of body reservoirs during and after antibiotic treatment.
- Super-infections with resistant pathogens during and after antibiotic treatment.
- Any bacterial super-infection during antibiotic treatment.
- Development of resistance in the index pathogen.
- In relevant studies, change in resistance in the population.

Interpretation of results:

- If resistance-related outcomes are different between the arms of the trial, discuss the implications for policy and practice.
- If no data are available, discuss what is known about resistance to the drugs of interest from other sources, and how it can influence policy and practice.